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(57) Abstract

A solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to a an extent of 35 % or more by weight of the dosage form, characterised in that the carrier material further includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes. Such rapidly disintegrating compositions are particularly valuable in the treatment of pain and fever.

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DOSAGE FORM OF IBUPROFEN

This invention relates to a non-effervescent compressed solid dosage form for oral administration, to a process to make said dosage form and to its therapeutic utility.

Ibuprofen, namely 2-(4-isobutylphenyl)propionic acid, is a well known medicament with analgesic, anti-inflammatory and anti-pyretic properties. It is usually sold in the form of racemic ibuprofen (equal amounts of the S(+)-ibuprofen and R(-)-ibuprofen enantiomers). It may also be in the form of the purified form of either enantiomer, especially S(+)-ibuprofen which is acknowledged to be the active form of racemic ibuprofen. Ibuprofen is also available in salt form, for example the sodium salt of ibuprofen. Ibuprofen is available under prescription in the UK (eg Brufen (RTM)), primarily for the treatment of painful and anti-inflammatory disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, postoperative pain, post partum pain and soft tissue injuries, generally at doses up to 3200mg per day. Ibuprofen is also available as a non-prescription drug in the UK (eg Nurofen (RTM)), primarily for the treatment of symptoms of pain and fever including headache, migraine, rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea, dental pain and colds and flu, generally at doses up to 1200mg per day. A unit dose of ibuprofen or derivative thereof is generally equivalent to 200mg, 400mg, 600mg or 800mg racemic ibuprofen.

A major issue in connection with the above disorders is to improve the onset of action of ibuprofen, particularly in the treatment of pain. It is believed that rapid disintegration of a formulation releases the drug into the body quickly leading to a more rapid onset of therapeutic action compared with a standard dosage form. Accordingly, it is desired to produce a solid dosage form for oral administration adapted to disintegrate quickly in the gastro-intestinal tract. It is also preferred that the dosage form is manufactured by compression on standard tabletting machines with granulation and drying stages prior to tabletting optional. However, there are a number of formulation problems associated with providing a rapidly disintegrating

solid dosage form containing an ibuprofen medicament. One problem is that, in order to achieve a therapeutic dose, solid compositions generally contain a high dose of drug, eg 200-800mg ibuprofen, which thus forms a considerable proportion of the dosage form, ie greater than 35% by weight. Thus, there is a problem to include the ibuprofen medicament, together with the excipients useful to formulate the tablet into a dosage form and the excipients useful to ensure rapid disintegration, but also to provide a tablet that is both not too large for patient consumption and can be manufactured according to standard processes. Furthermore, the solid dosage form must be sufficiently hard to withstand the rigours of the manufacturing process, for example as encountered during the stage of film coating in a perforated rotating drum, and packaging etc, but must have appropriate disintegration characteristics to ensure rapid release of the drug from the formulation. Another desirable feature is that a composition comprising a mixture of the desired ingredients is capable of being compressed without sticking to the punches of the tabletting machine.

Previously, it has been found that a slight increase in the tabletting compaction pressure, in order to improve the hardness properties, led to a significant increase in the disintegration time of the resulting tablet. Thus, when compressing ingredients, it was difficult to use standard tabletting machine compaction pressures to arrive at an appropriate tablet disintegration time and maintain an acceptably sized tablet of sufficient hardness.

German Patent Application 3922441A seeks to improve the tablettability of ibuprofen compositions and discloses that this may be achieved by converting ibuprofen wholly or partially into its calcium salt and using these for tabletting. It is said that the compositions may optionally contain ibuprofen, S(+)-ibuprofen or their ammonium, sodium or potassium salts. The calcium salt and the optional other ibuprofen actives may be incorporated into the tablet as separately produced compounds or the salts may be formed in-situ during the tablet preparation method through the reaction between ibuprofen (an acidic drug) with a solution or suspension of a reactant comprising one or more of CaO, $Ca(OH)_2$, $CaCO_3$, NaOH, KOH, NH_4OH, Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, $(NH_4)_2CO_3$, NH_4HCO_3 (in an amount of 25% to 110% of the equivalent quantity of ibuprofen). The mixture obtained is then granulated, dried if appropriate, and then tabletted after the optional incorporation of

other excipients. The specification comments that depending on the proportions of other salts used with the calcium salt, the ammonium and alkali salts improve the solubility of the calcium salt-containing compositions and thus control the bioavailability, but they also increase the hygroscopicity and stickiness. These are both undesirable characteristics for optimum tabletting. This disclosure does not seek to improve the disintegration time.

We have now found that by incorporating an alkali metal carbonate or bicarbonate in the composition for compression, a solid dosage form of acceptable size containing an ibuprofen medicament can be produced which has a rapid disintegration time and satisfactory hardness. The present invention is based on the discovery that the addition of an alkali metal carbonate or bicarbonate enhances the compressibility of a composition containing a compressible filler in combination with a disintegrant component leading to a solid dosage form with valuable hardness and disintegration characteristics. The disclosure in German Patent Application 3922441A of compositions containing the calcium salt optionally with an ibuprofen sodium or potassium salt, formed in-situ in the presence of a liquid during tablet formation, are outside the scope of the present invention.

Accordingly, the present invention provides a solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

The term "ibuprofen medicament" covers ibuprofen, its S(+) and R(-)-enantiomers and mixtures thereof, salts, hydrates and other derivatives.

Crushing strength is a measure of the hardness of a compressed dosage form. It represents the pressure required to break the tablet. The crushing strength of the

solid dosage form may be measured by any machine adapted for this purpose, ie by squeezing the dosage form between two jaws and measuring the force required to break the tablet diametrically. Suitable Crushing Strength Testers are available from Monsanto, Erweka and Schleuniger (manual or automatic operation). The disintegration time represents the time taken for the tablet to disintegrate in an aqueous medium under the test defined in the European Pharmacopoeia 1986 Ref V.5.1.1 (updated 1995).

Alkali metal carbonates and bicarbonates are not normally used as compressible materials. It was not expected that replacing a proportion of a compressible filler component in the composition with a portion of substantially incompressible alkali metal carbonate or bicarbonate would lead to a solid dosage form having both good crushing strength properties and good disintegration properties. It was also found that other soluble materials such as lactose, sucrose, mannitol, sodium citrate and sodium chloride did not yield tablets having the combination of satisfactory compressibility, crushing strength and disintegration properties and acceptable size, as is achieved by the use of the alkali metal carbonates or bicarbonates in a dosage form according to the present invention.

Alkali metal carbonates and bicarbonates are soluble materials which have previously been proposed for use in effervescent tablets, for example to react with the acid component in an effervescent couple (see for example WO 94/10994) or to prevent initiation of the effervescent reaction eg during storage. Effervescent tablets disintegrate by means of the reaction between acid and base particularly in the presence of water leading to the production of carbon dioxide. The system of disintegration of non-effervescent dosage forms according to the present invention, which are arranged to be swallowed and for which an effervescent reaction is not desired, is different to that of effervescent systems. The present dosage form does not contain any soluble acidic component with which the alkali metal carbonate or bicarbonate could react in an effervescent reaction.

Sodium bicarbonate is also known for use as an antacid and has previously been combined with ibuprofen in a tablet formulation for its antacid properties, eg Japanese Patent Application 63198620A. However, this document does not provide a

disclosure relating to the incorporation of ibuprofen and sodium bicarbonate in a tablet with a compressible filler component combined with a disintegrating component or the formation of solid dosage forms having the crushing strength and disintegration properties that are characteristic of the present invention.

Sodium bicarbonate has also been proposed for use in a water-soluble composition which forms an acceptably-tasting drink product comprising ibuprofen (33-46% w/w), L-arginine (34-51%) and sodium bicarbonate (9-29%) (US 4834966). However, this disclosure does not disclose the other formulation ingredients useful to provide the crushing strength and disintegration characteristics of the present invention.

US 4873231 relates to decreasing the toxicity of an ibuprofen salt by combining the salt with from one to five molar excess of a bicarbonate or carbonate. Example 13 discloses that sodium ibuprofen is pressed into a tablet with one equivalent of sodium or potassium bicarbonate to provide a dosage of 200 or 400mg ibuprofen. It gives no further details of the formulation and therefore does not provide an enabling disclosure concerning the production a solid dosage form having the crushing strength and disintegration properties which characterises the present invention.

European Patent Application 418043A discloses that although the compounds selected from alkali metal bicarbonates, alkali metal monohydrogen phosphates and alkali metal tribasic citrates can be used to mask the taste of a water-soluble ibuprofen salt in solution, other materials including alkali metal carbonates cannot be used, because, in potential taste-masking amounts, the resultant aqueous solution has an unacceptably high pH for oral administration. The compositions used therein will usually be in the form of a free-flowing powder suitably contained in unit dose sachets. However, it is also disclosed that the composition could be in any other form such as a water-soluble tablet suitable for dissolution in water which can include a small amount of an effervescent couple to assist dispersion of the tablet on addition to water. However, there is no disclosure of a non-effervescent solid dosage form characterised by the crushing strength and disintegration properties according to the present invention.

The present invention allows any ibuprofen medicament to be formulated into a solid dosage form using a carrier material common to all ibuprofen medicaments. Due to the different properties of the different ibuprofen medicaments, such as the melting point, the crystal form, particle size, the yield pressure etc, it is difficult to find a common carrier material which allows all forms of ibuprofen to be compressed into a solid dosage form. Accordingly, where prior art disclosures particularly relate to formulation characteristics required of an ibuprofen dosage form and/or to compression into a solid dosage form, in many cases the disclosure relates particularly either to ibuprofen or to an ibuprofen salt. For example, European Patent Application 298666A, WO 90/08542, WO 89/02266 and US Patent 4609675, all relate to directly compressible formulations containing ibuprofen as the active ingredient, but do not extend their disclosures to salts. Thus, it is a particular advantage that the dosage form according to the invention may include both ibuprofen and salts thereof, particularly salts such as the sodium salt, where compression into a dosage form is particularly difficult.

The alkali metal carbonate or bicarbonate enhances the compressibility of the compressible filler in combination with the ibuprofen medicament. Thus, the use of an alkali metal carbonate or bicarbonate allows a reduction in the amount of compressible filler component that would normally be required in a composition to achieve satisfactory compressibility. This is of advantage as ibuprofen medicaments are usually administered in large doses. Thus minimising the amount of formulation excipients is valuable as it allows an acceptably sized dosage form to be produced. In accordance with the invention, the total amount of the compressible filler and alkali metal carbonate or bicarbonate that can be used is less than the amount of compressible filler component combined with a disintegrating component that would be required in the absence of the alkali metal carbonate or bicarbonate to achieve a dosage form with satisfactory hardness and disintegration characteristics.

The solid dosage forms according to the invention are adapted for direct administration to a patient to obtain the desired therapeutic effect. They are not intended to be dissolved or dispersed in water prior to administration. Furthermore, the compressed dosage forms according to the present invention need no further

processing after compression of a composition comprising a mixture of the ingredients to produce a solid dosage form.

The ibuprofen molecule exists in two enantiomeric forms and the term ibuprofen medicament as used herein is intended to embrace the individual enantiomers, especially S(+)-ibuprofen, and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as racemic ibuprofen. The ibuprofen medicament may be also present in the form of any salt or other derivative of ibuprofen or its enantiomers. If necessary, the ibuprofen medicament may comprise one or more ibuprofen active ingredients such as racemic ibuprofen and S(+)-ibuprofen in combination. However, we prefer that the ibuprofen medicament comprises a single ibuprofen active ingredient. The ibuprofen medicament may also be present in different degrees of hydration. The present invention applies to both anhydrous and hydrated forms, for example the monohydrate or the dihydrate. The most stable anhydrous or hydrated form will generally be used. Preferably, the ibuprofen medicament is in the form of a salt of racemic or S(+)-ibuprofen. Representative examples include alkali metal salts, for example the sodium or potassium salts of ibuprofen; alkaline earth metal salts, eg the calcium or magnesium salts of ibuprofen; metal salts, eg the aluminium salt of ibuprofen; amino acid salts for example the lysine or arginine salts of ibuprofen; or amine salts, eg the meglumine salt of ibuprofen. Preferably the ibuprofen medicament is a single salt selected from alkali metal salts, amino acid salts and amine salts. Greater advantages are obtained in accordance with the present invention by the use of soluble salts of ibuprofen, for example the alkali metal salts such as sodium and potassium, as these materials are poorly compressible. For example, the sodium salt is a flaky, soft and sticky material. It does not lend itself to formulation into a dosage form as it is particularly difficult to compress. It is also difficult to pre-granulate the sodium salt prior to compression with other excipients into tablets. It thus usually requires an initial treatment stage such as milling, in order to form satisfactory tablets. However, no such pre-treatment of the sodium salt is required in accordance with the present invention. It is thus a further advantage to use sodium ibuprofen taken from a bulk production process to produce the raw material. These soluble ibuprofen salts also have the advantage that, as they are more soluble in an aqueous medium, on release from the formulation they have improved absorption, thus leading to an improved

onset of action compared to the substantially insoluble forms of ibuprofen. The sodium salt of ibuprofen is particularly preferred, especially the sodium salt of racemic ibuprofen. It has been found that the dihydrate of the sodium salt of racemic ibuprofen is a particularly stable hydrated form, accordingly we prefer to use the sodium salt dihydrate in a compressed dosage form according to the present invention.

The particle size of the ibuprofen medicament should be such as to facilitate the manufacturing process, for example to permit flow during the manufacturing process and thus aid the compression process. Accordingly, preferably it has a median particle size in the range 25-600μm, preferably 50-300μm, most preferably 150-250μm.

It is generally desired to have as high a proportion of ibuprofen medicament in the dosage form as possible to reduce the size of the solid dosage form. Representative dosage forms generally comprise ibuprofen medicament to an extent to give 35-90% ibuprofen by weight of the formulation, preferably 35-75% by weight, more preferably 40-60% by weight and most preferably 45-55% by weight. Unit dosages may comprise ibuprofen medicament to an extent of 50mg, 100mg, 150mg, 200mg, 250mg, 300mg, 350mg, 400mg, 500mg, 600mg and 800mg. Where salts or other derivatives are employed, usually the precise unit doses are chosen to give the equivalent ibuprofen doses set out above, for example 256mg of the sodium salt dihydrate or 342mg of the dl lysine salt provides an equivalent dose to 200mg ibuprofen.

The alkali metal carbonate or bicarbonate aids the formation of a solid dosage form having the crushing strength and disintegration characteristics outlined above. The alkali metal carbonate or bicarbonate is suitably included in the dosage form in solid form. It is not necessary to dissolve it in a solvent, eg water, for a granulation step before compression into a solid dosage form. The properties of crushing strength and disintegration of the dosage form are achieved by the presence of the solid alkali metal carbonate or bicarbonate in homogenous admixture with the ibuprofen medicament and compressible filler with disintegrating component. It is

particularly desired that the particles of the ibuprofen medicament and alkali metal carbonate or bicarbonate are intimately mixed.

The alkali metal carbonate or bicarbonate used in accordance with the present invention may suitably comprise sodium carbonate or bicarbonate or potassium carbonate or bicarbonate either alone or mixed together. Preferably, the alkali metal comprises sodium, thus sodium bicarbonate and sodium bicarbonate are preferred ingredients. The alkali metal carbonates may be supplied anhydrous or in varying degrees of hydration for example the monohydrate and decahydrate. Both these forms may be used. However, we prefer to use the anhydrous form. The preferred alkali carbonate for use in accordance with the present invention is thus anhydrous sodium carbonate.

The alkali metal carbonate or bicarbonate is present to aid the formation of the ibuprofen medicament dosage form and to provide a solid dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes. Suitably, the alkali metal carbonate or bicarbonate is present in an amount of 3-20% by weight of the dosage form, preferably 4-16% by weight, more preferably 5-15% by weight and most preferably 6-10% by weight of the dosage form. The alkali metal carbonate or bicarbonate preferably has a particle size in the range of 25-600μm, more preferably 50-100μm. In preferred dosage forms the weight of sodium carbonate or bicarbonate to ibuprofen medicament is in the range 1:2 to 1:10 parts by weight. In a particularly preferred aspect of the invention the dosage form is in the form of a directly compressed tablet comprising 40-85% w/w sodium salt of ibuprofen and 5-15% w/w sodium carbonate or bicarbonate.

The carrier material forms suitably up to 65% by weight of the dosage form. Preferred dosage forms include 25-65% by weight carrier material, more preferably 40-60% by weight and most preferably 45-55% by weight carrier material. In a more preferred dosage form, the ratio of ibuprofen medicament to the carrier material is in the range 2:1 to 1:2 parts by weight and the carrier material comprises 5-20% w/w sodium carbonate or bicarbonate.

The carrier material comprises a compressible filler component which is used in a sufficient amount together with the alkali metal carbonate or bicarbonate to ensure that the composition containing the ibuprofen medicament is capable of being formed, preferably by direct compression, into a solid dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes. The ingredients are usually compressed from a dry powder mixture. The mixture may contain a pre-granulated product, eg formed by wet or dry granulation and optionally containing the ibuprofen medicament, and the dry granule produced may be combined with other dry powder ingredients, as necessary, and compressed into a solid dosage form. Usually, in any wet pre-granulation stage, the ibuprofen medicament would be present in the granule. The alkali metal carbonate or bicarbonate would be added to the formed granule with optional other excipients, such as a lubricant, prior to compression. However, preferably no liquid (ie water) is added to the formulation in any optional pre-granulation stage or prior to compression. It will also be appreciated that a directly compressible formulation has advantages as it represents a more efficient tabletting process, namely just mixing the ingredients and then compressing them, thus alleviating the need for the intermediate granulation and drying steps necessary in other tabletting procedures.

The compressible filler component is suitably present to an extent of 10-50% by weight of the dosage form, preferably 20-50% by weight of the dosage form, more preferably 27-45% by weight, most preferably 30-40% by weight of the dosage form. The ratio of alkali metal carbonate or bicarbonate to compressible filler component is preferably in the range 2:1 to 1:10 parts by weight.

Examples of the compressible filler component include one or more of cellulose derivatives, starch and derivatives thereof (eg pre-gelatinised starch), soluble sugars (eg lactose, sucrose, dextrin), sodium chloride, calcium phosphate, calcium sulphate, mannitol, sorbitol, cyclodextrin and maltodextrin. Preferably the compressible filler component comprises a cellulose derivative. Examples of suitable cellulose derivatives include methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate and micro-crystalline cellulose. The preferred cellulose derivative used in accordance with the present invention is micro-crystalline cellulose. Further

preferably, the cellulose derivative has a particle size above 100μm, preferably in the range 100-150μm.

In preferred dosage forms the cellulose derivative forms 50-100% by weight of the compressible filler component, more preferably 70-100% and most preferably 90-100% by weight of the compressible filler component. The remainder of the compressible filler component may be formed by other fillers known in the art including those listed above. Preferred compressible filler components comprise one or more of microcrystalline cellulose, lactose and mannitol. In a preferred aspect of the present invention, where the compressible filler component comprises 50-100% by weight of a cellulose derivative, the ratio of alkali metal carbonate or bicarbonate to cellulose derivative is suitably in the range of 2:1 to 1:10, more preferably 1:1 to 1:9 and especially 1:3 to 1:8 parts by weight. In a further preferred aspect the combined weight ratio of the cellulose derivative and alkali metal carbonate or bicarbonate to the ibuprofen medicament is 1:10 to 2:1 parts by weight, more preferably 1:4 to 2:1 parts by weight, most preferably 1:1 to 1:2 parts by weight.

The compressible filler component is combined with a disintegrating component. Examples of disintegrating components include one or more of wheat starch, maize starch, potato starch, sodium starch glycollate, low-substituted hydroxypropylcellulose, alginic acid, cross-linked polyvinylpyrrolidone, magnesium aluminium silicate and croscarmellose sodium. Preferred disintegrants comprise one or more of croscarmellose sodium and sodium starch glycollate. Such disintegrating agents, if used, may form up to 15% by weight of the dosage form, for example 1-10% by weight, preferably 5-15% by weight of the dosage form. Some compressible filler components have disintegrant properties, for example microcrystalline cellulose and/or hydroxypropylmethyl cellulose and therefore a discrete disintegrant material is not necessary as the compressible filler component is thus combined with a disintegrating component. However, we prefer to use a compressible filler component (which may have disintegrant properties) and a discrete disintegrant component which are separate components mixed into the composition.

In a particularly preferred dosage form the carrier material comprises 8-80% by weight compressible filler component (more preferably 50-75% by weight), 8-40% by weight alkali metal carbonate or bicarbonate (more preferably 10-20% by weight), 10-20% by weight disintegrant (more preferably 12-18% by weight). Especially preferred is a carrier material comprising 50-75% microcrystalline cellulose, 12-18% croscarmellose sodium and 8-20% sodium carbonate or bicarbonate. Desirably the ratio of the compressible filler to the alkali metal carbonate or bicarbonate to the disintegrant component is 1-9:1:0.5-2 parts by weight, preferably 2.5-6:1:0.8-1.4 parts by weight.

The compressed dosage form may also comprise one or more inert diluents (which are not characterised by the property of compressibility) as desired by the person skilled in the art. The inert diluent may be present up to an extent of 20% by weight of the formulation, suitably 0-10% by weight.

The solid dosage form may also include a flow aid such as talc or colloidal silicon dioxide, which may preferably be used to an extent of up to 4% by weight of the formulation, for example 0.5-2.0% by weight of the formulation. Lubricants such as stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, calcium stearate, sodium stearyl fumarate or magnesium stearate may also be included in the dosage form. These may be used to an extent of up to 4% by weight of the dosage form, for example 0.5-2% by weight of the dosage form. Anti-adherents such as talc may further be included in an amount of up to 4% by weight of the dosage form, for example 0.5-2% by weight of the dosage form.

A solid dosage of the invention may be coated, eg with a sugar or film coating which has minimal effect on the disintegration time. A preferred solid dosage form of the present invention, ie a tablet, is film coated, such as by spraying tablets with a solution comprising hydroxypropylmethylcellulose and a plasticiser such as propylene glycol, polyethylene glycol and/or talc in one or more coatings.

A preferred dosage form comprises:-

(a) 40-60% by weight sodium salt of ibuprofen (more preferably 45-55% by weight);

(b) 20-50% by weight of a compressible filler, eg micro-crystalline cellulose (more preferably 30-40% by weight);

(c) 4-16% by weight sodium carbonate or sodium bicarbonate (more preferably 5-10% by weight);

(d) Up to 10% by weight of a disintegrant, eg croscarmellose sodium or sodium starch glycollate (more preferably 5-10% by weight);

(e) Up to 4% by weight of a lubricant, eg stearic acid (more preferably 0.5-2.0% by weight); and

(f) Up to 2% by weight of a flow aid, eg colloidal silicon dioxide (more preferably 0.5-1% by weight).

In a further preferred dosage form the ratio of ibuprofen medicament to carrier material is in the range 1:2 to 2:1 parts by weight, preferably 2:3 to 3:2 parts by weight, and the ratio of the cellulose derivative compressible filler component to alkali metal carbonate or bicarbonate is 9:1 to 1:1, preferably 5:1 to 3:1 parts by weight.

A solid dosage form produced in accordance with the present invention may be compressed, preferably directly compressed, to have a crushing strength in the range of 6.5-15Kp, more preferably 8-12Kp. This can be achieved, for example, using standard single punch or rotary tabletting machines having a compression force in the range 100-140MPa.

It will be appreciated by the person skilled in the art that due to the different excipients used in the formulation and varying amounts thereof that for any compression pressure, different formulations will have different crushing strengths and disintegration times. Preferred dosage forms exhibit a crushing strength of 6.5-15Kp and a disintegration time of less than 10 minutes at a compression force above 80MPa. More preferred formulations exhibit a crushing strength of 6.5-15Kp

and a disintegration time of less than 10 minutes when compressed at a compression force in the range 100-140MPa such as by a standard tabletting machine, eg a rotary tabletting machine. Such compression pressures include, 110MPa, 120MPa and 130MPa. Especially preferred dosage forms exhibit a crushing strength of 6.5-15Kp and a disintegration time of less than 10 minutes when compressed at all pressures in the range 100-140MPa.

As disclosed hereinabove, it is necessary to have a dosage form of appropriate crushing strength. This is necessary so that the dosage form retains its integrity and does not crumble and/or break-up during the manufacturing process, the packaging process and transit of the packaged product. However, it is also necessary to ensure that the dosage form is not too hard that the drug cannot be released from the formulation quickly. Preferred dosage forms have a crushing strength in the range 7-12Kp, more preferably 8-12Kp. Preferably the dosage form has a crushing strength in the range 8-12Kp at a compression force in the range 100-140MPa.

The disintegration time of the tablet formed in accordance with the present invention is less than 10 minutes as measured by the method described in the European Pharmacopoeia 1986, Ref V.5.1.1 (updated 1995) (A. Disintegration Test for Tablets and Capsules). Preferred disintegration times are less than 6 minutes (eg 1-6 minutes), more preferably less than 5 minutes (eg 1-5 minutes) and most preferably 3 minutes or less (eg 1-3 minutes).

The dosage forms according to the present invention may or may not be water-soluble. We have found that water-solubility of the dosage form is not crucial. Some of the materials found to be most useful in accordance with the present invention are insoluble. Accordingly, if one or more materials is insoluble, the dosage form is water-insoluble and this represents a preferred dosage form.

The dosage forms formed in accordance with the present invention are prepared by compression. The carrier material is combined with the ibuprofen medicament and compressed (preferably directly compressed) into a solid dosage form. The final stage of producing the solid dosage form (eg compression) may be preceded by a pre-granulation stage such as initial wet-granulation or initial dry granulation. In the

wet granulation stage the ibuprofen medicament is generally pre-granulated with a binder, such as polyvinylpyrrolidone in a solvent, such as water or a hydrocarbon solvent and then the granules are dried. The granulated material is then mixed with other excipients as necessary and formed into a solid dosage form according to the invention. In any initial pre-granulation stage however, there is no requirement to add a solvent (eg water) at any stage during the manufacturing process and therefore, in a preferred embodiment of the invention, no drying stage is necessary. In a dry pre-granulation stage, certain of the components may be compressed together such as by roller compaction or slugging, and the granules are then mixed with the remaining excipients and compressed into a solid dosage form. The dosage forms may also be formed by sieving powdered ingredients into a container and then blending all of the ingredients to prepare a homogeneous mixture. The mixture may then be directly compressed to form tablets. This process forms a further aspect of the invention.

Thus, there is provided a process to prepare a non-effervescent solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a compressible filler component combined with a disintegrating component, characterised by combining the carrier material incorporating an alkali metal carbonate or bicarbonate with the ibuprofen medicament to form a homogeneous solid mixture under substantially dry conditions, optionally with other tabletting excipients, and compressing the mixture into one or more solid dosage forms having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

In a more preferred process, the dosage form is prepared by direct compression of a powder mixture of the ingredients and does not include any pre-granulation stage. In such a process the ibuprofen medicament may be combined with the compressible filler component, a discrete disintegrant component and the alkali metal carbonate or bicarbonate. The other optional carrier excipients. such as a flow aid and a lubricant, may also be added and mixed so that all the powder particles are in intimate admixture, and finally the mixture is directly compressed into a solid dosage form according to the present invention.

In a preferred process, there is provided a dosage form comprising the sodium salt of ibuprofen together with a carrier material comprising microcrystalline cellulose and sodium carbonate or bicarbonate.

In therapeutic use the dosage forms of the present invention are administered orally, thus the therapeutic dosage forms are presented in solid dosage form, preferably as a tablet. The dosage forms may be coated with a sugar or film coating, which dissolves substantially immediately the dosage form comes into contact with an aqueous medium. The composition may also be compressed onto a solid core of another material to form a solid formulation with an quick release outer coating. Alternatively, the compressed composition may be present in one or more layers of a multi-layer solid dosage form. In such formulations the remaining layers or core may comprise standard excipients to provide conventional, fast or slow release and are well within the knowledge of a person skilled in the art (eg, see Remington's Pharmaceutical Sciences, 17th Edition, Ed Gennaro et al).

Thus, in a further preferred aspect the invention also provides a solid formulation having a layer comprising a composition comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the composition and the carrier material comprising a compressible filler component combined with a disintegrating component characterised in that the carrier material comprises an alkali metal carbonate or bicarbonate in an amount such that the composition is capable of compression to provide a layer having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

The dosage forms of the present invention may, if desired, include other compatible pharmacologically active ingredients (for example centrally acting analgesics, eg codeine) and/or enhancing agents. Thus, for example, the dosage form may include any ingredient commonly used in a cough, cold or 'flu remedy, for example caffeine or another xanthine derivative, and/or another analgesic, and/or a skeletal muscle relaxant, and/or an antihistamine, and/or a decongestant, and/or a cough suppressant and/or an expectorant.

Suitable antihistamines include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cyproheptadine, dexbromopheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, tazifylline, temelastine, terfenadine, tripelennamine or triprolidine. Preferably non-sedating antihistamines are employed. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifenesin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

Ibuprofen and its derivatives are primarily anti-inflammatory, analgesic and anti-pyretic agents but have also been proposed for other therapeutic uses, including the treatment of periodontal bone loss, pruritus and Alzheimer's disease. The dosage forms of the present invention are therefore indicated for use in the treatment of all therapeutic uses for which ibuprofen is effective, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, seronegative arthropathies, periarticular disorders and soft tissue injuries. They may also be used in the treatment of postoperative pain, postpartum pain, dental pain, dysmenorrhoea, headache, migraine, rheumatic pain, muscular pain, backache, neuralgia and/or musculoskeletal pain or the pain or discomfort associated with the following: respiratory infections, colds or influenza, gout or morning stiffness.

In a further aspect the present invention provides a method of obtaining an onset-hastened analgesic and/or anti-pyretic response comprising the administration of a non-effervescent compressed solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate or bicarbonate, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

In yet a further preferred aspect, the invention provides the use of an alkali metal carbonate or bicarbonate in a carrier material including a compressible filler component combined with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament under substantially dry conditions and then for compression into a solid non-effervescent dosage form wherein the ibuprofen medicament comprises 35% or more by weight of the dosage form, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

The preparation of compressed tablets from formulations of the present invention is illustrated by the following Examples. In the Examples the racemic ibuprofen and racemic/S(+)-ibuprofen sodium salt is available from Knoll Pharma, Nottingham, GB; the grades of microcrystalline cellulose are available from the FMC Corporation, Brussels, BE under the tradenames Avicel PH101 and PH102; Croscarmellose sodium is available from the FMC Corporation, Brussels, BE under the tradename Ac-Di-Sol; colloidal silicon dioxide is available from Degussa, Frankfurt, DE under the tradename Aerosil 200; hydrogenated vegetable oil is available from Karlshamn, SE under the tradename Sterotex; hydroxypropylmethyl cellulose 2910 (50CPs) is available from Colorcon, Kent, GB; hydroxypropylmethyl cellulose 2910 (6CPs) is available from Shin-etsu, Japan and the Opaspray is available from Colorcon, Kent, GB; sodium starch glycollate is available from Edward Mendell, Reigate, GB, under the tradename Explotab; sodium stearyl fumarate is available from Forum Chemicals, Surrey, GB, under the tradename Pruv; mannitol is available from Roquette Freres, Lestrem, France, under the tradename Pearlitol, cross-linked polyvinylpyrrolidone is available from BASF, Ludwigshaven, Germany under the tradename Kollidon CL.

A. Method of Preparation of Tablets in the Examples

The tablets were prepared by screening all the ingredients and blending until an homogenous mixture was obtained using a conventional blending machine. The formulation was then fed into and compressed on a single punch tabletting machine (Manesty F) using a compression force in the range 100 to 140 MPa. In some Examples, (Examples 1-9, 22) the compositions were compressed at particular compression forces, eg 100, 120, 140 MPa. In other Examples (Examples 10-21, 23-27) the compositions were compressed at an appropriate compression force within the range 100-140 MPa having regard to the ingredients used and the crushing strength and dissolution time required of the finished tablet.

B. Measurement of the Properties of the Tablets Prepared in the Examples

1. Crushing Strength (Kp)

The crushing strength is a measure of the hardness of a tablet. It was measured by recording the diametrical crushing strength when the tablet was broken between the motorised jaws of a Schleuniger crushing strength tester. The range of crushing strengths of five tablets prepared with each Example formulation is given and the mean crushing strengths for Examples 10-27 are also given.

2. Disintegration Time (Minutes)

The disintegration time was measured using the disintegration method described in the European Pharmacopoeia 1986, Ref V.5.1.1 (updated 1995) using tap water (pH approximately 7) as the liquid. The method provides the time by which six tablets prepared with each Example formulation had all disintegrated.

C. Example Tablets and Properties Thereof

% are given in weight

Ibuprofen is racemic ibuprofen except where indicated

Examples 1-3

Ingredients	Example 1	Example 2	Example 3
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.2%	53.1%	51.2%
Microcrystalline cellulose (PH 101)	-	13.3%	12.8%
Microcrystalline cellulose (PH 102)	35.4%	-	-
Lactose NF (Spray Dried)	-	14.9%	8.0%
Anhydrous sodium carbonate	5.0%	10.4%	20.0%
Croscarmellose sodium	7.2%	7.5%	7.2%
Colloidal silicon dioxide	0.2%	-	-
Stearic acid	0.5%	0.8%	0.8%
Magnesium stearate	0.5%	-	-

Properties of Tablet	Example 1		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	10.4-10.7	10.7-11.5	10.3-11.2
Disintegration Time (min)	5.8	5.4	5.0

Properties of Tablet	Example 2		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.8-9.2	7.2-10.8	9.3-11.0
Disintegration Time (min)	3.5	3.5	4.5

Properties of Tablet	Example 3		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.5-9.5	9.3-10.4	11.1-11.7
Disintegration Time (min)	4.3	4.7	4.9

Examples 4-6

Ingredients	Example 4	Example 5	Example 6
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	53.1%	53.1%	51.2%
Microcrystalline cellulose (PH 101)	13.3%	13.3%	12.8%
Lactose NF (Spray Dried)	14.9%	14.9%	14.4%
Anhydrous sodium carbonate	10.4%	10.4%	10.0%
Croscarmellose sodium	7.5%	7.5%	7.2%
Stearic acid	-	-	0.8%
Magnesium stearate	0.8%	-	-
Hydrogenated Vegetable Oil	-	0.8%	-
Talc	-	-	3.6%

Properties of Tablet	Example 4		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	6.6-7.2	8.3-10.2	8.8-10.1
Disintegration Time (min)	4.7	5.4	5.3

Properties of Tablet	Example 5		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	6.6-6.9	8.5-9.1	9.0-10.7
Disintegration Time (min)	2.9	3.2	3.7

Properties of Tablet	Example 6		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.1-8.6	9.7-10.5	10.7-11.6
Disintegration Time (min)	3.5	3.9	4.5

Examples 7-9

Ingredients	Example 7	Example 8	Example 9
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.2%	51.2%	51.2%
Microcrystalline cellulose (PH 101)	27.2%	-	-
Microcrystalline cellulose (PH 102)	-	35.4%	29.6%
Anhydrous sodium carbonate	10.0%	5.0%	10.0%
Croscarmellose sodium	7.2%	7.2%	7.2%
Colloidal silicon dioxide	-	0.2%	1.0%
Stearic acid	1.0%	1.0%	0.5%
Magnesium stearate	-	-	0.5%
Talc	3.4%	-	-

Properties of Tablet	Example 7		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	7.0-7.4	8.1-9.1	7.9-10.4
Disintegration Time (min)	3	3.8	4.5

Properties of Tablet	Example 8		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.4-9.1	10.1-10.6	12.2-12.7
Disintegration Time (min)	3.1	4.1	4.8

Properties of Tablet	Example 9		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	5.8-6.2	7.3-7.9	9.2-9.8
Disintegration Time (min)	2.2	3.3	4.7

Examples 10 and 11

Ingredients	Example 10	Example 11
Content of drug per tablet (mg)	256mg	256mg
Ibuprofen sodium salt dihydrate	49.7%	51.2%
Microcrystalline cellulose (PH 101)	-	12.8%
Microcrystalline cellulose (PH 102)	34.3%	-
Lactose	-	8.0%
Anhydrous sodium carbonate	7.8%	-
Sodium bicarbonate BP	-	20.0%
Croscarmellose sodium	7.0%	7.2%
Colloidal silicon dioxide	0.2%	-
Stearic acid	1.0%	0.8%

Properties of Tablet	Example 10	Example 11
Compression force (MPa)	100-140	100-140
Crushing Strength Range (Kp)	7.1-8.0	8.2-9.2
Mean Crushing Strength (Kp)	7.5	8.8
Disintegration Time (min)	4.3	6.0

The tablet core of Example 10 was coated with the following coatings (% are given of core weight):-

First coat: hydroxypropylmethyl cellulose 2910 (6Cps) (1.016%), talc (0.204%), Opaspray White M-I-7111B (0.336%).

Outer coat: hydroxypropylmethylcellulose 2910 (5-0Cps) (0.437%), Polyethylene Glycol 6000 (0.049%), calcium stearate (0.002%).

The disintegration time of the coated tablet of Example 10 was 5.5 minutes.

Examples 12-14

Ingredients	Example 12	Example 13	Example 14
Content of drug per tablet (mg)	**256mg**	**256mg**	**256mg**
Ibuprofen sodium salt dihydrate	51.7%	49.7%	49.7%
Microcrystalline cellulose (PH 102)	35.7%	34.3%	34.3%
Anhydrous sodium carbonate	4.0%	-	7.8%
Sodium bicarbonate - BP	-	7.8%	-
Croscarmellose sodium	7.3%	7.0%	-
Sodium starch glycollate	-	-	7.0%
Colloidal silicon dioxide	0.3%	0.2%	0.2%
Stearic acid	1.0%	1.0%	1.0%

Properties of Tablet	Example 12	Example 13	Example 14
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength range (Kp)	7.7-9.1	8.7-9.6	5.7-7.1
Mean Crushing Strength (Kp)	8.7	9.1	6.0
Disintegration Time (min)	3.5	4.5	5.8

The tablet cores of Examples 12-14 had the same coatings applied as described in Example 10. The disintegration times were 5.1 min, 5.5 min and 7.5 mins respectively for Examples 12, 13 and 14.

Examples 15-17

Ingredients	Example 15	Example 16	Example 17
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.7%	49.7%	51.2%
Microcrystalline cellulose (PH 102)	35.7%	34.3%	35.4%
Anhydrous sodium bicarbonate	4.0%	-	5.0%
Sodium bicarbonate	-	7.8%	-
Croscarmellose sodium	-	-	7.2%
Sodium starch glycollate	7.3%	7.0%	-
Colloidal silicon dioxide	0.3%	0.2%	0.2%
Stearic acid	1.0%	1.0%	-
Sodium stearyl fumarate	-	-	1.0%

Properties of Tablet	Example 15	Example 16	Example 17
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength Range (Kp)	6.2-8.1	6.4-7.2	10.0-11.6
Mean Crushing Strength (Kp)	6.9	6.7	10.7
Disintegration Time (min)	5.5	4.9	4.8

Examples 18-20

Ingredients	Example 18	Example 19	Example 20
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	50.7%	51.2%	51.2%
Microcrystalline cellulose (PH 101)	-	12.8%	12.8%
Microcrystalline cellulose (PH 102)	35.0%	-	-
Lactose NF (Spray Dried)	-	14.4%	14.4%
Anhydrous sodium carbonate	5.9%	10.0%	10.0%
Croscarmellose sodium	7.1%	7.2%	7.2%
Colloidal silicon dioxide	0.3%	-	-
Stearic acid	1.0%	-	-
Hydrogenated Vegetable Oil	-	1.6%	1.0%
Talc	-	2.8%	3.4%

Properties of Tablet	Example 18	Example 19	Example 20
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength Range (Kp)	8.5-9.4	10.0-10.8	9.1-10.3
Mean Crushing Strength (Kp)	8.9	10.4	9.7
Disintegration Time (min)	4.8	3.9	5.7

Examples 21-23

Ingredients	Example 21	Example 22	Example 23
Content of drug per tablet (mg)	**256mg**	**256mg**	**200mg**
Ibuprofen sodium salt dihydrate	51.2%	49.7%	-
*Ibuprofen	-	-	49.7%
Microcrystalline cellulose (PH 101)	12.8%	-	-
Microcrystalline cellulose (PH 102)	-	34.3%	34.3%
Mannitol 300	14.4%	-	-
Anhydrous sodium carbonate	10.0%	7.7%	7.8%
Croscarmellose sodium	7.2%	7.0%	7.0%
Colloidal silicon dioxide	-	0.3%	0.2%
Stearic acid	1.0%	0.5%	1.0%
Magnesium stearate	-	0.5%	-
Talc	3.4%	-	-

* 50µm crystal size

Properties of Tablet	Example 21
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	8.9-9.7
Mean Crushing Strength (Kp)	9.4
Disintegration Time (min)	4.0

Properties of Tablet	Example 22		
Compression force (MPa)	100	120	140
Mean Crushing Strength (Kp)	10.2	10.5	10.5
Disintegration Time (min)	4.8	5.5	6.0

Properties of Tablet	Example 23
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	6.6-7.0
Mean Crushing Strength (Kp)	6.8
Disintegration Time (min)	0.6

Examples may also be prepared in a similar way to Examples 1-22 above containing the sodium salt of racemic ibuprofen in an amount of 64mg, 128mg, 192mg, 384mg, 512mg using the same proportions of ingredients as given in Examples 1-22.

Examples 24-26

Ingredients	Example 24	Example 25	Example 26
Content of drug per tablet (mg)	**342.0g**	**342.0g**	**342.0g**
Ibuprofen (dl lysine salt)	68.4%	49.7%	49.7%
Microcrystalline cellulose (PH 102)	20.35%	-	-
Hydroxypropylmethylcellulose	-	34.3%	-
Tricalcium phosphate	-	-	34.3%
Anhydrous sodium carbonate	5.0%	7.8%	7.8%
Croscarmellose sodium	5.0%	-	-
Cross-linked polyvinyl pyrrolidone	-	7.0%	7.0%
Colloidal silicon dioxide	0.25%	0.2%	0.2%
Stearic acid	1.0%	1.0%	1.0%

Properties of Tablet	Example 24		
Compression force (MPa)	100	120	140
Crushing Strength (Kp)	6.0	7.0	8.0
Disintegration Time (min)	4.0	4.5	4.8

Properties of Tablet	Example 25	Example 26
Compression force (MPa)	100-140	100-140
Crushing Strength Range (Kp)	9.0-13.8	10.5-10.8
Mean Crushing Strength (Kp)	11.3	10.6
Disintegration Time (min)	8.0	7.5

Tablets may also be prepared in a similar manner to Examples 24-26 above containing the ibuprofen dl lysine salt in an amount of 171.0mg, 256.5mg and 513.0mg using the same proportions of ingredients as given in Examples 24-26.

Example 27

Ingredients	Example 27
Content of drug per tablet (mg)	256g
S(+)-Ibuprofen sodium salt dihydrate	49.7%
Microcrystalline cellulose (PH 102)	34.3%
Anhydrous sodium carbonate	7.8%
Croscarmellose sodium	7.0%
Colloidal silicon dioxide	0.2%
Stearic acid	1.0%

Properties of Tablet	Example 27
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	7.3-8.7
Mean Crushing Strength (Kp)	7.9
Disintegration Time (min)	4.3

Comparative Examples

A. Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

Ingredient	Comparative Formulation A (without (bi)carbonate component) % (wt)
Ibuprofen sodium salt dihydrate	53.9%
Microcrystalline cellulose (PH102)	37.2%
Croscarmellose sodium	7.6%
Colloidal silicon dioxide	0.3%
Stearic acid	0.5%
Magnesium stearate	0.5%

B. Tablets containing 342.0mg racemic ibuprofen lysine salt
(Ibuprofen equivalent 200mg)

Ingredient	Comparative Formulation B (without (bi)carbonate component) % (wt)
Ibuprofen (dl lysine salt)	69.9
Microcrystalline cellulose (PH102)	23.4
Croscarmellose sodium	5.3
Colloidal silicon dioxide	0.4
Stearic acid	1.0

In the Figures, Figure 1 shows a comparison of the disintegration times of:-

(a) a compressed dosage form of the present invention containing the sodium salt of ibuprofen (Example 22) with comparative Example A (without a (bi)carbonate component); and

(b) a compressed dosage form of the present invention containing the lysine salt of ibuprofen (Example 24) with comparative Example B (without a (bi)carbonate component).

The disintegration times are shown as a function of compaction pressure.

Figure 2 shows a comparison of the disintegration properties of the tablets having the following components with no sodium carbonate (Comparative Formulation A) and varying amounts of sodium carbonate additionally included in that Example (as shown below). The disintegration time is shown as a function of the compaction pressure.

Ingredient	Comparative Formulation A wt (mg)	Ex 28 wt (mg)
Ibuprofen sodium salt dihydrate	256.00	256.00
Microcrystalline cellulose (PH 102)	176.75	176.75
Anhydrous sodium carbonate	-	12.50
Croscarmellose sodium	36.00	36.00
Colloidal silicon dioxide	1.25	1.25
Stearic acid	2.50	2.50
Magnesium stearate	2.50	2.50

Ingredient	Ex 29 wt (mg)	Ex 30 wt (mg)	Ex 31 wt (mg)
Ibuprofen sodium salt dihydrate	256.00	256.00	256.00
Microcrystalline cellulose (PH 102)	176.75	176.75	176.75
Anhydrous sodium carbonate	25.00	37.50	50.00
Croscarmellose sodium	36.00	36.00	36.00
Colloidal silicon dioxide	1.25	1.25	1.25
Stearic acid	2.50	2.50	2.50
Magnesium stearate	2.50	2.50	2.50

It can be seen from Figures 1 and 2 that at standard operating compaction pressures in the range 100-140MPa, the disintegration time of the tablet without sodium carbonate steeply rises reflecting a sharp increase in disintegration time for only a small increase in compaction pressure. The disintegration time vs compaction force gradient for tablets containing sodium carbonate is unexpectedly much more shallow which leads to the processing advantages described herein. In Figure 2 it can be seen that the disintegration times at 100MPa for tablets containing sodium carbonate are less than 300 seconds, whereas omitting this component provides a disintegration time greater than 420 seconds.

Claims

1. A solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not contain a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

2. A dosage form according to claim 1 wherein the ibuprofen medicament is in the form of a salt of ibuprofen.

3. A dosage form according to claim 2 wherein the ibuprofen medicament is the sodium salt of racemic ibuprofen.

4. A dosage form according to any one of claims 1 to 3 comprising a filler component and a discrete disintegrant component.

5. A dosage form according to any one of claims 1 to 4 comprising 5-15% w/w alkali metal carbonate or bicarbonate.

6. A dosage form according to any one of claims 1 to 5 wherein the alkali metal carbonate or bicarbonate comprises sodium carbonate or sodium bicarbonate.

7. A dosage form according to claim 6 comprising sodium carbonate or bicarbonate in a weight ratio to the ibuprofen medicament of 1:2 to 1:10.

8. A dosage form according to any one of claims 1 to 7 wherein the compressible filler component comprises one or more of microcrystalline cellulose, lactose and mannitol.

9. A dosage form according to any one of claims 1 to 8 wherein the disintegrant comprises one or more of croscarmellose sodium and sodium starch glycollate.

10. A dosage form according to any one of claims 1 to 9 in the form of a compressed tablet.

11. The use of an alkali metal carbonate or bicarbonate in a carrier material including a compressible filler component combined with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament under substantially dry conditions and then for compression into a solid non-effervescent dosage form wherein the ibuprofen medicament comprises 35% or more by weight of the dosage form, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

12. The use according to claim 11 wherein the ibuprofen medicament is in the form of the sodium salt.

13. The use according to either one of claims 11 and 12 wherein the carrier material is adapted for direct compression with the ibuprofen medicament into a tablet.

14. The use according to any one of claims 11 to 13 wherein the solid dosage form comprises the sodium salt of ibuprofen together with a carrier material comprising microcrystalline cellulose and sodium carbonate or bicarbonate.

15. The use according to anyone of claims 11 to 14 wherein carrier material comprises 45-60% microcrystalline cellulose, 2-10% croscarmellose sodium and 2-20% sodium carbonate or bicarbonate.

16. A method of obtaining an onset-hastened analgesic and/or anti-pyretic response comprising the administration of a non-effervescent compressed solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate or bicarbonate, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of

less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

17. A method according to claim 16 wherein the dosage form has a crushing strength in the range 8-12Kp, at a compression force in the range 100-140MPa.

18. A method according to either one of claims 15 and 16 wherein the solid dosage form has a disintegration time in the range 1-5 minutes.

19. A method according to any one of 16 to 19 wherein the dosage form is in the form of a directly compressed tablet comprising 40-85% w/w sodium salt of ibuprofen and 5-15% w/w sodium carbonate or bicarbonate.

20. A process to prepare a non-effervescent solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a compressible filler component combined with a disintegrating component, characterised by combining the carrier material incorporating an alkali metal carbonate or bicarbonate with the ibuprofen medicament to form a homogeneous solid mixture under substantially dry conditions optionally with other tabletting excipients and compressing the mixture into one or more solid dosage forms having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

21. A process according to claim 20 wherein the ibuprofen medicament is a salt of racemic ibuprofen.

22. A process according to either one of claims 20 and 21 wherein the carrier material comprises a inert diluent component.

23. A process according to any one of claims 20-22 wherein the dosage form is prepared by direct compression of a powder mixture of the ingredients and does not include any pre-granulation stage.

24. A process according to any one of claims 20-23 wherein the ratio of the alkali metal carbonate or bicarbonate to compressible filler component is in the range 2:1 to 1:10 parts by weight.

25. A process according to any one of claims 19-24 wherein the ratio of ibuprofen medicament to the carrier material is in the range 2:1 to 1:2 parts by weight and the carrier material comprises 5-20% w/w sodium carbonate or bicarbonate.

26. A solid formulation having a layer comprising a composition comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the composition and the carrier material comprising a compressible filler component combined with a disintegrating component characterised in that the carrier material comprises an alkali metal carbonate or bicarbonate in an amount such that the composition is capable of compression to provide a layer having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

Figure 1 Ibuprofen Salts

Effect of sodium carbonate on disintegration time

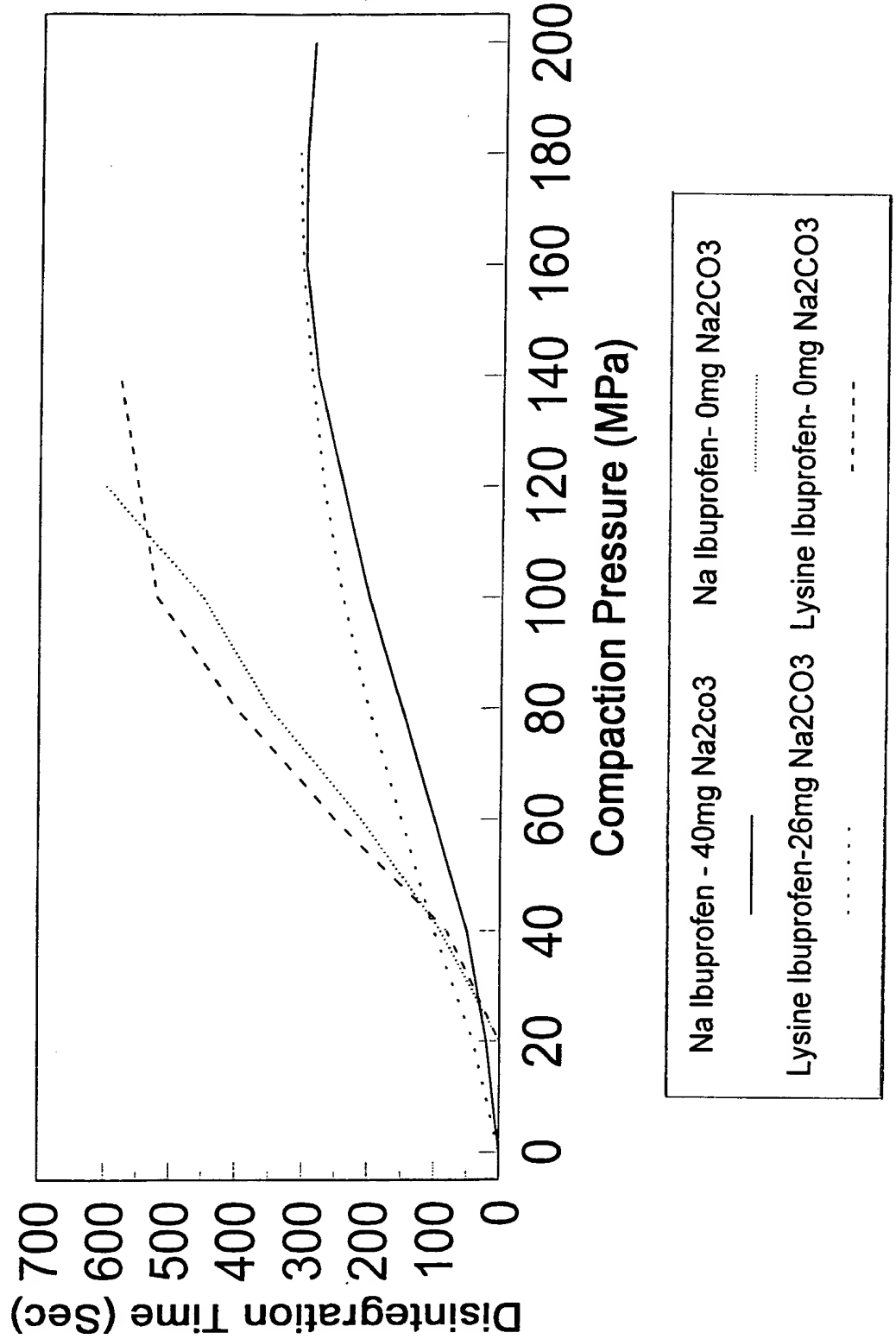
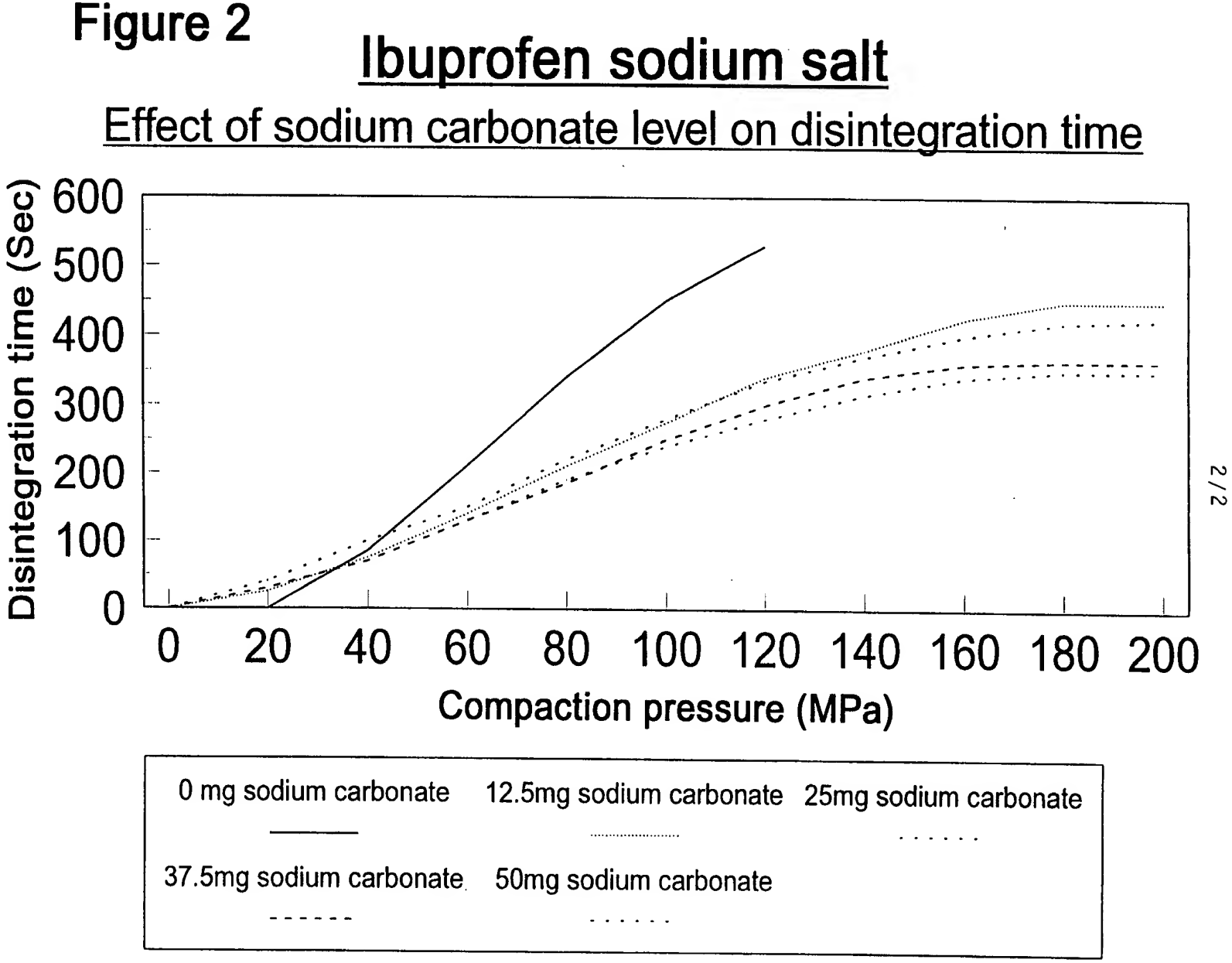


Figure 2


Ibuprofen sodium salt
Effect of sodium carbonate level on disintegration time
Disintegration time (Sec)
600
500
400
300
200
100
0
0
20
40
60
80
100
120
140
160
180
200
Compaction pressure (MPa)
0 mg sodium carbonate
12.5mg sodium carbonate
25mg sodium carbonate
37.5mg sodium carbonate
50mg sodium carbonate

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP 97 / 00841

International Filing Date 19 FEB 1997 (19. 02. 97)

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P/559

Box No. I TITLE OF INVENTION

Therapeutic Composition

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

The Boots Company PLC
1 Thane Road West
Nottingham
NG2 3AA
United Kingdom

☐ This person is also inventor.

Telephone No. 0115-950-6255

Facsimile No. 0115-959-4599

Teleprinter No.

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PRICE Ian Ashley
The Boots Company PLC
1 Thane Road West
Nottingham
NG2 3AA
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: GB

State *(i.e. country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SMITH Elizabeth Jane
The Boots Company PLC
Group Patents Department
Building D31, 1 Thane Road West
Nottingham. NG2 3AA
United Kingdom

Telephone No. 0115-959-4585

Facsimile No. 0115-959-4599

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes: at least one must be marked)*:

Regional Patent

- ☒ AP ARIPO Patent: KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
- ☒ EE Estonia .....
- ☒ ES Spain .....
- ☒ FI Finland .....
- ☒ GB United Kingdom
- ☒ GE Georgia .....
- ☒ HU Hungary .....
- ☒ IL Israel .....
- ☒ IS Iceland
- ☒ JP Japan .....
- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg .....
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....
- ☐ .....
- ☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____.

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) GB	21 February 1996 (21-02-96)	9603699.1	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☐ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA /_____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request.*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	: 3	sheets
2. description	: 31	sheets
3. claims	: 4	sheets
4. abstract	: 1	sheets
5. drawings	: 2	sheets
Total	: 41	sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☒ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☒ priority document(s) *identified in Box No. VI as item(s):*
5. ☐ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

E.J.Smith
SMITH Elizabeth Jane

For receiving Office use only

1. Date of actual receipt of the purported international application: 19 FEB 1997 (19.02.97)
2. Drawings: ☒ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P/559		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 97/00841	19/02/1997	21/02/1996
Applicant		
THE BOOTS COMPANY PLC et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established by this Authority to read as follows:

   DOSAGE FORM OF IBUPROFEN

5. With regard to the **abstract,**
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/00841

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16-19
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/00841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 607 467 A (SPIRIG AG PHARMAZEUTISCHE PRAE) 27 July 1994 see page 3, line 31 - line 39 see page 3, line 45 - line 49 see page 4, line 9 - line 14 see page 10; example 9 ---	1,4-6, 8-10, 16-18,26
X	WO 93 23026 A (PHARMATRANS SANAQ AG ;GEISSLINGER GERD (DE); BRUNE KAY (DE); BAUER) 25 November 1993 see page 6 - page 7; examples 1,2 --- -/--	1,3-5,7, 9-11,13, 16-18, 20,22, 23,26

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
7 August 1997	21. 08. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 89 02266 A (MALLINCKRODT INC) 23 March 1989 cited in the application see the whole document	1
A	EP 0 478 838 A (PHARMATRANS SANAQ AG) 8 April 1992 cited in the application see claim 1	1

INTERNATIONAL SEARCH REPORT

mation on patent family members

rnational Application No
PCT/EP 97/00841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0607467 A	27-07-94	FI 935380 A	02-06-94
		JP 6239738 A	30-08-94
		US 5631296 A	20-05-97
WO 9323026 A	25-11-93	DE 4216756 A	25-11-93
		CA 2136071 A	25-11-93
		EP 0641200 A	08-03-95
		JP 7506583 T	20-07-95
		US 5565613 A	15-10-96
WO 8902266 A	23-03-89	US 4837031 A	06-06-89
		AU 2385188 A	17-04-89
		CA 1309351 A	27-10-92
		DE 3877764 A	04-03-93
		EP 0377658 A	18-07-90
EP 0478838 A	08-04-92	DE 3922441 A	17-01-91

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P/559		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 97/00841	19/02/1997	21/02/1996
International Patent Classification (IPC) or national classification and IPC		
A61K31/19		
Applicant		
THE BOOTS COMPANY PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/09/1997	9. 03. 98
Name and mailing address of the IPEA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D.J.M. Telephone No. 02546

Form PCT/IPEA/409 (cover sheet) (January 1994) (03/10/1997)

PCT'ed

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP97/00841

I. Basis of the report

1. This report has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*

☒ the international application as originally filed

☐ the description, pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

☐ the claims, Nos. , as originally filed
Nos. , as amended under Article 19
Nos. , filed with the demand
Nos. , filed with the letter of

☐ the drawings, sheets / fig. , as originally filed
sheets / fig. , filed with the demand
sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.

☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty	Claims	2,3,7,12,14,15,19,21,25,	YES
	Claims	1,4-6,8-11,13,16-18,20,22-24,26	NO
Inventive Step	Claims		YES
	Claims	1-26	NO
Industrial Applicability	Claims	1-15,16-19*,20-26	YES
	Claims		NO

2. Citations and Explanations

* see point 4. below

1. Reference is made to the following documents:
D1 : EP-A-607467
D2 : WO-A-9323026

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1, 4-11, 13, 16, 17, 18, 20, 22-24, 26 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

The document D1 discloses a solid non effervescent composition, obtained by combining under "substantially" dry conditions ibuprofen, a filler, a disintegrating component and an alkali salt, like a carbonate or bicarbonate, for a hastened analgesic-antipyretic effect (see D1, page 2, l. 1-6, p. 3, l. 31-33, p. 7-10, examples 1,2, and 9). Ibuprofen is released at more than 90% in less than 10 minutes (see D1, Fig. 8, corresponding to example 9), which therefore means that the disintegration time of the tablet is less than 10 minutes, and also that, even if D1 does not mention it, the crushing strength must be comprised between 6.5-15 Kp. The alkali salt of carbonate disclosed in D1 is particularly used to accelerate the release of the active agent (see D1, page 3, l. 31-33 and l. 45-54). Consequently, unless the Applicant is able to prove or explain the difference between the compositions disclosed in D1 and the compositions of the present Application, the subject-matter of Claims 1, 4, 5, 6, 8-11, 13, 16, 17, 20, 22, 24, 26 is not new over D1 (Article 33(2) PCT.

The document D2 relates to a solid non-effervescent tablet obtained by direct compression of

ibuprofen, a filler, namely calcium carbonate, and a disintegrating agent. This tablet has the property to disintegrate promptly (see D2 page 6, l. 19-25, p. 7, example 3; p. 4, 2nd par.). Even if the parameters of crushing strength and disintegration time are not disclosed in D2, the release curves of Figure 2 corresponding to the formulation of example 1 from D2, and which contains calcium phosphate instead of calcium carbonate, make clear that the compositions disclosed in D2 have the same properties than the formulations of the present application, unless the Applicant is able to prove or explain the difference between the composition disclosed in example 3 of D2 and the compositions of the present application. Consequently, the subject-matter of Claims 1, 4, 9, 10, 11, 16, 17, 18, 20, 22, 23, 24, 26 is not new over D2 (Article 33(2) PCT).

3. The documents D1 and D2 are also of particular relevance as far as inventive step of Claims 1, 11, and 26, as far as novel, is concerned (Article 33(3) PCT). These documents solve indeed the same problem, namely making a fast release form or ibuprofen with as less excipients as possible, so that even, in this case, if novelty can be restored, the present application does apparently not fulfill the requirements of Article 33(3) PCT over prior art documents D1 and D2.
The same applies for the subject-matter of Claim 20, which relates to a conventional process for the production of the compositions, and Claim 16, which relates to a conventional use of such compositions, which claims do not contain any feature which could be considered as inventive per se, and could therefore be considered as inventive only when they are in relation with a composition claim which fulfills the requirements of Article 33(3) PCT.

Dependent Claims 2,3,7,12,14,15,19,21, 25 do not in themselves contain inventive features, because the choice of a particular form or salt of ibuprofen, or of a particular filler or disintegrating agent, as well as particular ratios or concentrations of the components, are normal design options for a skilled man.

4. For the assessment of the present Claims 16-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VII. **Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

2. Claims 1, 11, 16, 20 and 26 do meet the requirements of Rule 6.3(b) PCT, whereby the features known from documents D1 or D2 should be placed in the preamble.
The documents D1 and D2 disclose solid compressed dosage forms which comprise an alkali metal salt of carbonate or bicarbonate which are also included in independent claims 1, 11, 16, 20, and 26 of the present application.

3. The units Kp expressed in Claims 1, 11, 16, 17, 20, 26 and in the description do not meet the requirements of Rule 10.1 (a) PCT.
It is also not clear if the units MPa are Mega Pascals.

4. The term Opaspray used on page 23 appears to be a registered trade mark and should have been identified as such.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The various definitions of the invention given in independent Claims 1 and 26 are such that the claims as a whole are not clear and concise, contrary to Article 6 PCT and Rule 6.4(a)-(c) PCT.

2. The whole subject-matter of Claims 15 and 19 has been omitted from the description. Consequently, claims 15 and 19 do not meet the requirements of Article 6 PCT.

3. The subject-matter of Claim 4 is redundant with Claim 1, because all the feature of dependent Claim 4 are already present in independent Claim 1. Claim 4 does therefore not meet the requirements of Article 6 PCT.

4. The term "substantially" in Claims 11 and 20 is vague and indefinite and, as such, renders the scope of the claims unclear; accordingly, the claim do not meet the requirements of Article 6 PCT.

PATENT COOPERATION TREATY

PCT

REC'D 11 MAR 1998
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P/559		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 97/ 00841	19/02/1997	21/02/1996
International Patent Classification (IPC) or national classification and IPC		
A61K31/19		
Applicant		
THE BOOTS COMPANY PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications and corresponding pages relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☒ Certain defects in the international application

   VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/09/1997	09.03.98
Name and mailing address of the IPEA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Boulois, D.J.M. Telephone No. 02546

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP97/00841

I. Basis of the report

1. This report has been drawn up on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*

☒ the international application as originally filed

☐ the description, pages , as originally filed
pages , filed with the demand
pages , filed with the letter of

☐ the claims, Nos. , as originally filed
Nos. , as amended under Article 19
Nos. , filed with the demand
Nos. , filed with the letter of

☐ the drawings, sheets / fig. , as originally filed
sheets / fig. , filed with the demand
sheets / fig. , filed with the letter of

2. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.

☐ the drawings, sheets / fig.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2 (c)).

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty	Claims	2,3,7,12,14,15,19,21,25,	YES
	Claims	1,4-6,8-11,13,16-18,20,22-24,26	NO
Inventive Step	Claims		YES
	Claims	1-26	NO
Industrial Applicability	Claims	1-15,16-19*,20-26	YES
	Claims		NO

2. Citations and Explanations

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1. Reference is made to the following documents:

D1 : EP-A-607467

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2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of Claims 1, 4-11, 13, 16, 17, 18, 20, 22-24, 26 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

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3. The documents D1 and D2 are also of particular relevance as far as inventive step of Claims 1, 11, and 26, as far as novel, is concerned (Article 33(3) PCT). These documents solve indeed the same problem, namely making a fast release form or ibuprofen with as less excipients as possible, so that even, in this case, if novelty can be restored, the present application does apparently not fulfill the requirements of Article 33(3) PCT over prior art documents D1 and D2.
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